Editorial

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Non-alcoholic fatty liver – Perhaps not so benign

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The defining histological feature of non-alcoholic fatty liver disease (NAFLD) is lipid droplets within hepatocytes. There are however, a range of histological changes that may accompany hepatic steatosis including combinations of lobular and/or portal inflammation, hepatocyte ballooning and fibrosis. The significance of these accompanying histological changes, is that they help define the clinical course of the patient. Early studies demonstrated a dichotomy in outcomes based upon the presence or absence of non-alcoholic steatohepatitis (NASH). Follow-up of patients with biopsy proven hepatic steatosis without inflammation or ballooning (termed 'bland steatosis'), reveals a remarkably benign course with very few individuals progressing to cirrhosis or dying from liver disease [1,2]. In contrast, patients with ballooning, Mallory hyaline or fibrosis (i.e. NASH) are more likely to progress to cirrhosis and die from its complications [3,4]. Accordingly, the current management guidelines for NAFLD revolve around determining the presence or absence of NASH. In the presence of NASH, liver specific pharmacotherapy should be considered in addition to lifestyle changes involving weight loss and exercise [5,6]. If NASH is excluded, then lifestyle interventions alone are recommended. This paradigm suggests that patients with bland steatosis or steatosis with non-specific inflammation (collectively termed non-alcoholic fatty liver or NAFL) do not develop a 'second pathological hit' and remain within the same histological spectrum of disease over time. Although this notion was challenged 10 years ago [7], there is a paucity of knowledge regarding whether non-NASH (a.k.a. NAFL) can progress and thus acquire the prognostic and management implications that are associated with NASH.

Two studies published in the *Journal of Hepatology* have provided further insight into the natural history of NAFLD and challenge the dogma that NAFL is non-progressive. In this issue, McPherson and colleagues carefully evaluated 108 patients with NAFLD who underwent paired liver biopsies over a median interval of 6.6 years [21]. Twenty-seven of the 108 patients that had NAFL (steatosis alone or with mild inflammation), 10 (37%) developed fibrosis, with 6 (22%) of these having bridging fibrosis on follow-up biopsy. Interestingly, the proportion of patients who had progressive fibrosis was not different between patients who had NAFL or NASH (37% *vs.* 43%, $p = 0.6$). In a previous issue of the *Journal*, Pais *et al.* described a similar phenomena in a cohort of 70 NAFLD patients who underwent paired liver biopsies; among 25 subjects with NAFL at baseline, 16/25 (64%) progressed to NASH and 6 (24%) developed bridging fibrosis over a mean of 3.7 years [8]. Thus collectively, these studies suggest that NAFL may clearly progress, with one quarter of patients developing bridging fibrosis over a relatively short time period.

This data needs to be treated with some caution as there are clear limitations and caveats to studies where subjects have undergone serial liver biopsies. Although a proportion of follow-up biopsies may be performed as part of clinical trials, they are generally performed for clinical reasons such as suspicion of progressive disease, thereby creating bias. Furthermore, sampling error with liver biopsies leads to the possibility of misclassification, as does variability in pathologist interpretation which is particularly problematic for features such as inflammation and ballooning [9]. Therefore larger numbers to overcome the variance associated with sampling error, and robust histological evaluation and classification will be required for future studies. While keeping in mind the heterogeneity of distribution of histological lesions in NAFLD, two of the results from the British study are striking. First, eight out of 10 patients with steatosis and non-specific inflammation evolved towards full-blown steatohepatitis, while only 2 regressed towards bland steatosis. While this might still be due to sampling variability, it may more likely reflect a real trend in disease progression. Equally striking is the rate of spontaneous NASH resolution: only six of 81 patients with steatohepatitis at baseline no longer had steatohepatitis at follow-up. Whether one or several of these 6 patients actually improved their metabolic condition in between biopsies thus explaining the clearance of steatohepatitis is unknown. Yet, this very low figure stresses the "stability" of steatohepatitis as a pathological finding in the absence of therapeutic intervention. It thus strengthens "resolution of NASH" as a non-labile surrogate outcome for clinical trials in general and pivotal registration studies in particular [10,11].

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Abbreviations: NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; NAFL, non-alcoholic fatty liver.

The probability that NASH resolves as a chance finding appears to be very low.

Although these studies have demonstrated progressive liver injury among subjects with NAFL, how do we reconcile these paired biopsy studies with the benign outcomes for NAFL patients from longitudinal cohort studies previously mentioned? Are these patients actually at risk of liver related morbidity and mortality? The risk is clearly low but not negligible, with up to 6% of subjects with bland steatosis dying from liver disease over 8–20 years of follow-up. It is notable that the average age of these cohorts was between 40–50 years at baseline. Although it is unknown when these individuals acquired NAFLD, we do know that currently one in seven adolescents have NAFLD in developed countries [12]. Thus these adolescents will potentially have five or more decades of 'exposure' to NAFL. Assuming the risk of progressive liver disease is time-dependent, the burden of end-stage liver disease associated with NAFL could be substantial.

If progressive liver fibrosis can occur across the entire histological spectrum of NAFLD, are we able to predict patients who will progress? A variety of features associated with NASH including necro-inflammation, ballooning and Mallory-Denk bodies have been associated with progressive fibrosis or a higher fibrosis progression rate in systematic reviews as well as a large series from the NASH CRN, published in abstract form [13–15]. Although these cohorts have included predominantly NASH patients, it appears inflammation may also be associated with a differential rate of histological progression within the spectrum of NAFL. Within the McPherson and Pais cohorts, subjects with bland steatosis were less likely to develop NASH or progressive fibrosis than those with steatosis and mild inflammation. Although these differences were not statistically significant in either study due to the low numbers, this gradient of risk has also been noted in other cohorts [16,17]. Therefore, liver mortality rates for NAFL subjects with mild inflammation may be higher than those with bland steatosis. Furthermore, when McPherson and colleagues looked at just NAFL subjects, baseline steatosis grade was higher in those with progressive fibrosis, suggesting the prognostic importance of different histological features may differ according to the stage of liver disease.

Unfortunately, baseline clinical parameters have limited utility in predicting patients who will have progressive disease. In the McPherson study, the biochemical algorithm FIB-4 (composed of age, AST, ALT, and platelet count) was higher among subjects who had progressive fibrosis, although its accuracy to predict these individuals remained poor. However, both studies demonstrated that body weight and diabetes prevalence increased in parallel with progressive liver injury. Thus subjects with evidence of liver injury and inflammation and perhaps severe steatosis in the case of NAFL, are at greater risk of histological progression, as are those with worsening metabolic disease. Interestingly, this latter point is corroborated by a large series of 270 early-stage NAFLD patients (stages 0 to 2) with follow-up liver biopsies collected by the NASH CRN [18]. Fibrosis progression towards bridging fibrosis occurred in 16% over a median of 4.4 years. Crude predictors of progression were type 2 diabetes, the metabolic syndrome, a high HOMA score indicative of insulin resistance. Collectively, those converging observations are important because the metabolic state of a patient can be monitored. Persistence or worsening of metabolic risk factors should alert us to the possibility of disease progression. The current studies suggest that this also applies to patients with early disease including NAFL. A closer follow-up of this subset of NAFL individuals is therefore legitimate and should focus on detecting disease progression, either by non-invasive procedures or by liver biopsy. This is clearly different from current patterns of practice.

How do we translate these findings to the large proportion of the population who have NAFLD? Although this data suggests all NAFLD patients are at potential risk of progressive liver disease over a long period, recent studies have shown that fibrosis remains the best histological predictor of liver related complications and overall death [19,20]. In the largest series to date presented in abstract form, stages 2–4 fibrosis were the only histological features predictive of cirrhosis related complications in 619 individuals followed for a median of 12.7 years [20]. Thus overall, NAFLD is slowly progressive and the majority of individuals will not progress to cirrhosis or liver related death. Nevertheless, among patients with NAFL, which was previously considered to be benign, approximately one quarter may develop liver fibrosis. The development of fibrosis heralds an increased risk of morbidity associated with cirrhosis and death. The challenge remains how to best identify these patients and effectively treat them.

Conflict of interest

The authors who have taken part in this editorial declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

Authors contributions

LAA and VR both contributed equally to the data review and interpretation for this editorial, the manuscript writing and editing.

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